Clinical trial results:
A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)

Summary

EudraCT number	2019-000833-37
Trial protocol	DE GB IE DK FR BE ES NL IT
Global end of trial date	16 December 2022

Results information

Result version number	v2 (current)
This version publication date	02 February 2024
First version publication date	01 July 2023
Version creation reason	• New data added to full data set Addition of secondary end points to maintain consistency with CT.gov.

Trial information

Trial identification

Sponsor protocol code	VX18-445-110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04058366
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States,
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2022
Global end of trial reached?	Yes
Global end of trial date	16 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of VX-445/tezacaftor (TEZ)/ivacaftor (IVA) in subjects with cystic fibrosis who are heterozygous for the F508del mutation and a gating (F/G) or residual function (F/RF) mutation.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	34 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	United States: 81
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Canada: 12
Worldwide total number of subjects	251
EEA total number of subjects	112

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	22
Adults (18-64 years)	224
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects from parent study VX18-445-104 (NCT04058353) were enrolled in this study. A total of 251 subjects were enrolled in this study.

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part A: ELX/TEZ/IVA

Arm description:

Subjects received ELX (elexacaftor) 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 96 weeks.

Arm type	Experimental
Investigational medicinal product name	Elexacaftor/Tezacaftor/Ivacaftor
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	ELX/TEZ/IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed dose combination (FDC) once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 1	Part A: ELX/TEZ/IVA
Started	251
Completed	215
Not completed	36
Commercial drug is available for subjects	6
Other	6
Death	1
Adverse event	14
Other non-compliance	2

Withdrawal of Consent (not due to AE)	7

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part B: ELX/TEZ/IVA

Arm description:

Subjects received ELX 200 mg qd /TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Elexacaftor/Tezacaftor/Ivacaftor
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	ELX/TEZ/IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed dose combination (FDC) once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 2[1]	Part B: ELX/TEZ/IVA
Started	84
Completed	1
Not completed	83
Commercial drug is available for subjects	81
Physician decision	1
Withdrawal of Consent (not due to AE)	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total 251 subjects were enrolled from the parent study on Part A. However, only 84 subjects rolled over to Part B from Part A of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Part A
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 96 weeks.	

Reporting group values	Part A	Total	
Number of subjects	251	251	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	37.9		
standard deviation	± 14.4	-	
Gender categorical Units: Subjects			
Female	124	124	
Male	127	127	
Ethnicity Units: Subjects			
Hispanic or Latino	9	9	
Not Hispanic or Latino	224	224	
Not collected per local regulations	18	18	
Race Units: Subjects			
White	225	225	
Black or African American	2	2	
Other	5	5	
Not collected per local regulations	18	18	
More than one race	1	1	

End points

End points reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX (elexacaftor) 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 96 weeks.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd /TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 48 weeks.	

Primary: Part A : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Part A : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1]
End point description:	
Safety set included all subjects who received at least 1 dose of study drug in the treatment period.	
End point type	Primary
End point timeframe:	
From Baseline up to Week 100	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned. No statistical comparisons were planned for the Part A primary safety endpoint.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	251			
Units: Subjects				
Subjects with TEAEs	241			
Subjects with SAEs	38			

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[2]
End point description:	
Safety set included all subjects who received at least 1 dose of study drug in the treatment period.	
End point type	Primary

End point timeframe:

From Baseline up to Week 52

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned. No statistical comparisons were planned for the Part B primary safety endpoint.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Subjects				
Subjects with TEAEs	62			
Subjects with SAEs	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change from Parent Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

End point title	Part A: Absolute Change from Parent Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. The OL Full Analysis Set (OL-FAS) for Part A is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label study. This analysis set included study 104 parent study subjects who received Control IVA or TEZ/IVA and ELX/TEZ/IVA. Here "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 96

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	176			
Units: percentage points				
least squares mean (confidence interval 95%)				
Control-IVA or TEZ/IVA: Change at Week 96 (n=80)	4.1 (2.5 to 5.7)			
ELX/TEZ/IVA: Change at Week 96 (n=96)	3.7 (2.2 to 5.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change From Parent Study Baseline in Sweat Chloride (SwCl)

End point title	Part A: Absolute Change From Parent Study Baseline in Sweat Chloride (SwCl)

End point description:

Sweat samples were collected using an approved collection device. The OL Full Analysis Set (OL-FAS) for Part A is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label study. This analysis set included study 104 parent study subjects who received Control IVA or TEZ/IVA and ELX/TEZ/IVA. Here, "n signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 96

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	186			
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)				
Control-IVA or TEZ/IVA: Change at Week 96 (n=90)	-23.0 (-25.8 to -20.1)			
ELX/TEZ/IVA: Change at Week 96 (n=96)	-22.6 (-25.4 to -19.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change From Parent Study Baseline in Body Mass Index (BMI)

End point title	Part A: Absolute Change From Parent Study Baseline in Body Mass Index (BMI)

End point description:

BMI was defined as weight in kilogram (kg) divided by height in square meter (m^2).The OL Full Analysis Set (OL-FAS) for Part A is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label study. This analysis set included study 104 parent study subjects who received Control IVA or TEZ/IVA and ELX/TEZ/IVA. Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 96

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: kg/m^2				
least squares mean (confidence interval 95%)				
Control-IVA or TEZ/IVA: Change at Week 96 (n=97)	1.15 (0.84 to 1.45)			
ELX/TEZ/IVA: Change at Week 96 (n=110)	0.83 (0.54 to 1.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change From Parent Study Baseline in BMI Z-score

End point title	Part A: Absolute Change From Parent Study Baseline in BMI Z-score

End point description:

BMI was defined as weight in kilogram (kg) divided by squared height in meters (m^2). The z-score is a statistical measure to describe whether a value was above or below the standard. A z-score of 0 is equal to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. The OL Full Analysis Set (OL-FAS) for Part A is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label study. This analysis set included study 104 parent study subjects who received Control IVA or TEZ/IVA and ELX/TEZ/IVA. Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 96

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: z-score				
least squares mean (confidence interval 95%)				
Control-IVA or TEZ/IVA: Change at Week 96 (n=7)	0.11 (-0.17 to 0.40)			
ELX/TEZ/IVA: Change at Week 96 (n=11)	0.40 (0.17 to 0.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change From Parent Study Baseline in Body Weight

End point title	Part A: Absolute Change From Parent Study Baseline in Body Weight

End point description:

The OL Full Analysis Set (OL-FAS) for Part A is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label study. This analysis set included study 104 parent study subjects who received Control IVA or TEZ/IVA and ELX/TEZ/IVA. Here, "Number Analyzed" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 96

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Kilogram (Kg)				
least squares mean (confidence interval 95%)				
Control-IVA or TEZ/IVA: Change at Week 96 (n=97)	3.6 (2.7 to 4.6)			
ELX/TEZ/IVA: Change at Week 96 (n=110)	2.9 (2.0 to 3.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change From Parent Study Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score

End point title	Part A: Absolute Change From Parent Study Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score

End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. The OL Full Analysis Set (OL-FAS) for Part A is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label study. This analysis set included study 104 parent study subjects who received Control IVA or TEZ/IVA and ELX/TEZ/IVA. Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 96

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	208			
Units: units on a scale				
least squares mean (confidence interval 95%)				
Control-IVA or TEZ/IVA: Change at Week 96 (n=97)	7.2 (4.1 to 10.4)			
ELX/TEZ/IVA: Change at Week 96 (n=111)	8.1 (5.1 to 11.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 through Safety follow-up (up to Week 100 for Part A and up to Week 52 for Part B)	
Adverse event reporting additional description:	
MedDRA 24.1 for Part A and MedDRA 25.1 for Part B	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1, 25.1

Reporting groups	
Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 96 weeks.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 48 weeks.	

Serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 251 (15.14%)	3 / 84 (3.57%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 251 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Epididymal cyst			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	3 / 251 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	2 / 251 (0.80%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 251 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 251 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	0 / 251 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 251 (0.80%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Aspergilloma			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			

subjects affected / exposed	2 / 251 (0.80%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	16 / 251 (6.37%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 25	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	223 / 251 (88.84%)	48 / 84 (57.14%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	16 / 251 (6.37%)	0 / 84 (0.00%)	
occurrences (all)	25	0	
Aspartate aminotransferase increased			
subjects affected / exposed	16 / 251 (6.37%)	0 / 84 (0.00%)	
occurrences (all)	23	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	26 / 251 (10.36%)	1 / 84 (1.19%)	
occurrences (all)	26	1	
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	28 / 251 (11.16%)	0 / 84 (0.00%)	
occurrences (all)	46	0	
Nervous system disorders			

Headache			
subjects affected / exposed	71 / 251 (28.29%)	4 / 84 (4.76%)	
occurrences (all)	188	6	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	36 / 251 (14.34%)	2 / 84 (2.38%)	
occurrences (all)	43	2	
Fatigue			
subjects affected / exposed	40 / 251 (15.94%)	0 / 84 (0.00%)	
occurrences (all)	52	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 251 (5.18%)	2 / 84 (2.38%)	
occurrences (all)	15	4	
Constipation			
subjects affected / exposed	17 / 251 (6.77%)	1 / 84 (1.19%)	
occurrences (all)	26	1	
Diarrhoea			
subjects affected / exposed	48 / 251 (19.12%)	4 / 84 (4.76%)	
occurrences (all)	74	6	
Nausea			
subjects affected / exposed	28 / 251 (11.16%)	2 / 84 (2.38%)	
occurrences (all)	83	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	13 / 251 (5.18%)	1 / 84 (1.19%)	
occurrences (all)	15	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	65 / 251 (25.90%)	5 / 84 (5.95%)	
occurrences (all)	96	5	
Haemoptysis			
subjects affected / exposed	20 / 251 (7.97%)	5 / 84 (5.95%)	
occurrences (all)	44	9	
Dyspnoea			
subjects affected / exposed	29 / 251 (11.55%)	2 / 84 (2.38%)	
occurrences (all)	38	2	

Oropharyngeal pain			
subjects affected / exposed	42 / 251 (16.73%)	5 / 84 (5.95%)	
occurrences (all)	56	6	
Nasal congestion			
subjects affected / exposed	18 / 251 (7.17%)	1 / 84 (1.19%)	
occurrences (all)	22	1	
Sinus congestion			
subjects affected / exposed	15 / 251 (5.98%)	0 / 84 (0.00%)	
occurrences (all)	23	0	
Rhinorrhoea			
subjects affected / exposed	19 / 251 (7.57%)	0 / 84 (0.00%)	
occurrences (all)	20	0	
Productive cough			
subjects affected / exposed	17 / 251 (6.77%)	1 / 84 (1.19%)	
occurrences (all)	21	1	
Sputum increased			
subjects affected / exposed	34 / 251 (13.55%)	3 / 84 (3.57%)	
occurrences (all)	58	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	19 / 251 (7.57%)	0 / 84 (0.00%)	
occurrences (all)	22	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 251 (5.98%)	2 / 84 (2.38%)	
occurrences (all)	29	4	
Anxiety			
subjects affected / exposed	28 / 251 (11.16%)	1 / 84 (1.19%)	
occurrences (all)	31	1	
Depression			
subjects affected / exposed	16 / 251 (6.37%)	0 / 84 (0.00%)	
occurrences (all)	17	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	27 / 251 (10.76%)	2 / 84 (2.38%)	
occurrences (all)	33	2	

Back pain			
subjects affected / exposed	20 / 251 (7.97%)	2 / 84 (2.38%)	
occurrences (all)	20	2	
Myalgia			
subjects affected / exposed	16 / 251 (6.37%)	1 / 84 (1.19%)	
occurrences (all)	23	1	
Pain in extremity			
subjects affected / exposed	13 / 251 (5.18%)	0 / 84 (0.00%)	
occurrences (all)	18	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	52 / 251 (20.72%)	17 / 84 (20.24%)	
occurrences (all)	53	17	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	61 / 251 (24.30%)	17 / 84 (20.24%)	
occurrences (all)	102	26	
Upper respiratory tract infection			
subjects affected / exposed	15 / 251 (5.98%)	6 / 84 (7.14%)	
occurrences (all)	17	7	
Nasopharyngitis			
subjects affected / exposed	40 / 251 (15.94%)	7 / 84 (8.33%)	
occurrences (all)	60	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2021	Amended to extend the treatment Period by an additional 48 weeks (Part B)to evaluate the safety of ELX/TEZ/IVA beyond 96 weeks of treatment; Revised the statistical analysis section to reflect the updated study design; Clarified language regarding height measurement and ophthalmological examination timings for Parts A and B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported